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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,091	03/07/2008	Oliver Griesbeck	098832-0101	4598
22428	7590	12/29/2010	EXAMINER	
FOLEY AND LARDNER LLP			LONG, SCOTT	
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WASHINGTON, DC 20007			1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>
	10/567,091	GRIESBECK ET AL.
	<b>Examiner</b>	<b>Art Unit</b>
	SCOTT LONG	1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 06 December 2010.  
 2a) This action is **FINAL**.                    2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 27-60 is/are pending in the application.  
 4a) Of the above claim(s) 42-60 is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 27-41 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on 3/7/2008 is/are: a) accepted or b) objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | Paper No(s)/Mail Date. _____ .                                    |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>5/2/2007</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application |
|   | 6) <input type="checkbox"/> Other: _____ .                        |

## DETAILED ACTION

### ***Election/Restrictions***

Examiner acknowledges the election, with traverse, of Group I directed to a chimeric protein, in the reply filed on 6 December 2010. The applicant has further elected the species of chimeric protein comprising: (a) CFP as a first chromophore type; (b) human troponin C as a troponin type; and (c) YFP as a second chromophore type.

The applicant was requested to indicate whether a SEQ ID NO can be used to identify the elected species. In response, the Applicant has stated, “[a]s claim 41 is within Group I, Applicant’s also elect SEQ DI NO:2” (Remarks, filed 12/6/2010, page 4, parag.3). The applicant has avoided an explicit indication that SEQ ID NO: 2 corresponds to the elected species. Therefore, the examiner concludes that SEQ ID NO:2 does not correspond to the species of chimeric protein comprising: (a) CFP as a first chromophore type; (b) human troponin C as a troponin type; and (c) YFP as a second chromophore type. Therefore, SEQ ID NO:2 will not be specifically examined.

The applicant has traversed the restriction requirement by arguing MIYAWAKI ET AL: EP1238982 (published 11 September 2002), does not disclose troponin C/FRET chimeric polypeptides (Remarks, filed 12/6/2010, page 3, parag.3). The applicant further argues that accordingly, Miyawaki does not teach the technical features of claim 27 and the restriction is improper and should be withdrawn.

The examiner accepts the applicant's assertion that MIYAWAKI (EP1238982) may not anticipate the technical features of instant claim 27.

However, the examiner maintains that the restriction is proper because the technical features of instant claim 27 are taught by Miyawaki et al. (US2003/0017538). Miyawaki et al. (US2003/0017538) teaches a chimeric protein comprising cyan fluorescent protein + calmodulin + yellow fluorescent protein useful for FRET (parag. 0154). Therefore, Miyawaki suggests the genus of modified  $\text{Ca}^{2+}$ -binding (fusion) polypeptides comprising a) a first chromophore of a donor-acceptor-pair for FRET; b) a  $\text{Ca}^{2+}$ -binding polypeptide; and c) a second chromophore of a donor-acceptor-pair for FRET. Furthermore, Miyawaki et al. suggest that similar fusion proteins having variety of different  $\text{Ca}^{2+}$ -binding polypeptides could be made and Miyawaki particularly suggest troponin C as an example of  $\text{Ca}^{2+}$ -binding polypeptides which could be included in their invention (parag.0103). Therefore, Miyawaki et al suggest: a modified  $\text{Ca}^{2+}$ -binding (fusion) polypeptide comprising cyan fluorescent protein (CFP) + troponin C + yellow fluorescent protein (YFP) useful for FRET.

Miyawaki et al. does not specifically designate human, chicken or Drosophila troponin C as the calcium binding portion of their fusion protein. However, the claimed inventions lack unity of invention because even though the inventions of these groups require the technical feature of “human, chicken or Drosophila troponin C as the calcium binding portion of the fusion protein,” this technical feature is not a special technical feature as it does not make a contribution over the prior art in view of the generic troponin C/FRET chimeric polypeptide as taught by Miyawaki et al. in view of GAHLMANN et al (Journal of Biological Chemistry. 1990; 265(21): 12520-12528) which teaches the calcium-binding capacity of human troponin C.

MPEP 1801 indicates that lack of unity can be indicated "*a posteriori*." Accordingly, the examiner maintains that (lack of unity) restriction is proper over the pending claims. As the basis of the restriction is according to PCT rules, there is no basis for rejoining non-elected groups. At the examiner's discretion, the examiner may decide to rejoin nonelected groups at the time of allowance.

The applicant further traverses the species election requirement because "search and examination of the allegedly patentably distinct species is not unduly burdensome to the examiner." The examiner has demonstrated (below in the art rejections) that art can be provided with fails to provide for all claimed species, thereby demonstrating "undue burden." As the applicant has failed to indicate that all species are obvious over each other, the examiner finds his/her traversal unpersuasive. Accordingly, the examiner finds the applicant's argument unpersuasive.

### ***Claim Status***

Claims 27-60 are pending. Claims 1-26 are cancelled. However, claims 42-60 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 27-41 are under current examination.

***Sequence Compliance***

Sequence Listing and CRF have been received and are acknowledged by examiner. A statement that the Computer Readable Form (CRF) and the Sequence Listing are identical has been submitted and is acknowledged by examiner.

***Oath/Declaration***

The oath or declaration, having the signatures of all inventors, received on 4 August 2007 is in compliance with 37 CFR 1.63.

***Information Disclosure Statement***

The Information Disclosure Statements (IDS) filed on 11 May 2006 consisting of 7 sheets are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

***Priority***

This application claims benefit as a 371 of PCT/EP04/08739 (filed 08/04/2004) This application also claims benefit from EUROPEAN PATENT OFFICE (EPO) 03016691.2 (filed 08/04/2003). The instant application has been granted the benefit date, 4 August 2003, from the foreign application EPO 03016691.2

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyawaki et al. (US2003/0017538) in view of Gahlmann et al (Journal of Biological Chemistry. 1990; 265(21): 12520-12528).

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Claim 27 is directed to a modified Ca<sup>2+</sup>-binding polypeptide comprising:

- a) a first chromophore of a donor-acceptor-pair for FRET (Fluorescence Resonance Energy Transfer);
- b) a Ca<sup>2+</sup>-binding polypeptide with an identity of at least 80% to a 30 amino acid long polypeptide sequence of human troponin C or chicken skeletal muscle troponin C or drosophila troponin C isoform 1; and
- c) a second chromophore of a donor-acceptor-pair for FRET.

Miyawaki teaches Yellow Cameleon. Yellow Cameleon is a modified Ca<sup>2+</sup>-binding (fusion) polypeptide comprising cyan fluorescent protein (CFP) + calmodulin + lysine linker + M13 + yellow fluorescent protein (YFP) useful for FRET (page 10, col. 2, lines 3-6, parag. 0154). Therefore, Miyawaki suggests the genus of modified Ca<sup>2+</sup>-binding (fusion) polypeptides comprising a) a first chromophore of a donor-acceptor-pair for FRET; b) a Ca<sup>2+</sup>-binding polypeptide; and c) a second chromophore of a donor-acceptor-pair for FRET. Furthermore, Miyawaki et al. suggest that similar fusion proteins having variety of different Ca<sup>2+</sup>-binding polypeptides could be made and Miyawaki particularly suggest troponin C as an example of Ca<sup>2+</sup>-binding polypeptides which could be included in their invention (parag.0103). Therefore, Miyawaki et al suggest: a modified Ca<sup>2+</sup>-binding (fusion) polypeptide comprising cyan fluorescent protein (CFP) + troponin C + yellow fluorescent protein (YFP) useful for FRET.

Miyawaki fails to teach explicitly teach that the troponin C portion of the polypeptide of claim 27 is "human, chicken or Drosophila troponin C."

However, Miyawaki teach or suggest the limitations of dependent claims 28-34, because Miyawaki et al. suggest a FRET fusion protein having a donor/acceptor pair of CFP/YFP.

Regarding the limitations of claims 36-38 directed to fusion proteins further comprising localization signals, Miyawaki et al suggest these limitations (paragraphs 0075, 0095 and 0097).

Regarding the limitations of claims 39-40 directed to fusion proteins having certain functional characteristics, these do not further limit the structure of the claimed molecules. Therefore, they are intrinsic properties of the suggested fusion protein.

Regarding claim 39, the instant specification teaches that “the percent ration change of a protein, the fluorescence emission intensities of the FRET donor and the acceptor were measured at their respective emission maxima” (page 32, lines 4-6). Miyawaki et al. teach measuring the emission spectra of yellow cameleon (parag.0027). Therefore, performing this measurement of the suggested fusion protein is obvious to one of skill in the art reading the cited art.

Regarding claim 40, Miyawaki does not present data which performs titration curves to generate the Kd (dissociation constant) for Ca<sup>2+</sup> with the suggested fusion proteins. However, a skilled artisan studying measurements of intercellular calcium or monitoring calcium ion distribution would be interested in performing basic biochemical measurements on a newly made fusion protein. Therefore, making this measurement would be obvious to a skilled biochemist.

Gahlmann et al. teach the calcium-binding capacity of human troponin C.

Therefore, Gahlmann also suggest the limitations of claim 35.

Regarding the limitations of claim 41, directed to specific SEQ ID NOs which represent the certain embodiments of the polypeptides of claim 29, the cited art has provided teachings and rationale for making a polypeptide having the breath of the instant claims. Therefore, the cited art suggests the species of chimeric protein comprising: (a) CFP as a first chromophore type; (b) human troponin C as a troponin type; and (c) YFP as a second chromophore type. The applicant was requested to indicate whether a SEQ ID NO can be used to identify the elected species. The applicant has failed to explicitly indicate that SEQ ID NO: 2 corresponds to the elected species. However, since the species of claim 41 must contain the elements of claims 27-29, and these elements are suggested by the cited art, therefore, the specific SEQ ID NOs of claim 41 are suggested by the cited art.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to make a modified calcium-binding polypeptide comprising: (a) a first chromophor, (b) human troponin C, and (c) a second chromophor, having a FRET donor/acceptor pair.

Miyawaki et al. provides explicit teaching, suggestion and motivation to make a modified calcium-binding polypeptide comprising: (a) a first chromophor, (b) troponin, and (c) a second chromophor, having a FRET donor/acceptor pair.

The person of ordinary skill in the art would have been motivated to substitute one known, equivalent element for another to obtain predictable results. The claimed

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fusion proteins would have been obvious because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. In the instant case, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute human troponin C for the generic troponin C teaching of Miyawaki in the FRET polypeptide suggested by Miyawaki in view of Gahlmann because human troponin C is an embodiment which would have utility in a system using human cells and would be functionally equivalent to the generic "troponin C".

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Miyawaki et al. and Gahlmann et al. because the molecular biology required to substitute human troponin C for a generic troponin C was well established at the time of the instant invention.

Therefore the fusion proteins as taught by Miyawaki et al. in view of Gahlmann et al. would have been *prima facie* obvious over the fusion proteins of the instant application.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 39-40 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

In the present instance, claim 39 recites the broad recitation "more than 30%" [i.e., 30% to infinity], and the claim also recites "from 50% to 200%" which is the narrower statement of the range/limitation.

In the present instance, claim 40 recites the broad recitation "50 nM to 400  $\mu$ M," and the claim also recites "100 nM to 100  $\mu$ M," which is the narrower statement of the range/limitation.

### ***Conclusion***

No claims are allowed.

***Examiner Contact Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SCOTT LONG/  
Primary Examiner, Art Unit 1633